

**Figure 1: Human IRS-1 protein sequence (SEQ ID NO: 1)**

1 masppesdgf sdvrkvgylr kpksmhkrff vlraaseagg parleyyene kkwrhkssap  
61 krsiplescf ninkradskn khlvalytrd ehfaiaadse aeqdswyqal lqlhnrakgh  
5 121 hdgaaalgag ggggscsgss glgeagedls ygdvppgpaf kevwqvilkp kglgqtknli  
181 giyrlcltsk tisfvklInse aaavvlqlmn irrcghsenf ffievgrsav tgpgefwmqv  
241 ddsvvaqnmh etileamram sdefrprsk qsssnscnpi svplrhhln nppsqsqvglt  
301 rrsrtesita tspasmvggk pgsfrvrass dgegtmsrpa svdgspsvps tnrtahhrh  
361 gsarlhpln hrsipmpas rcspstspv slssstsg ghstsdclfr rssasvsgsp  
10 421 sdggfissde ygsspcdfsr sfrsvtpdsl ghppargee elsnyicmgg kgpstltapn  
481 ghyilrsgn ghrctpgtgi gtspalagde aasaadldnr frkrthsagt sptithqkt  
541 sqssvasiee ytemmpaypp gggsggrlpghrhsafvptr sypeeglemh plerrgghr  
601 pdsstlhtdd gympmspgva pvpsgrkgs dympmspksv sapqqiinpi rrpqrvdpn  
661 gymmmspsgg cspdigggps ssssssnv sgtsyglwt ngvgghshv lphpkppves  
15 721 sggklpctg dymnmispvgd ntsspsdcy ygpdpqhkp vlsyyslprs fkhtqrpgp  
781 eegarhqhlr lssgrlly aataddssss tssdsggy cgarleplp hphqvlqph  
841 lprkvdtaaq tnsrlarptr lsgdpkast lprareqqq qpllhppp kspgeyvnie  
901 fgdsqsgyls gpvafhssps vrcpsqlpa preeetgee ymkmdlgpgr raawqestgv  
961 emgrlgpapp gaasicrptr avpssrgdym tmqmscprqs yvdtspaapv syadmrtgia  
20 1021 aeevslprat maaassssaa sasptgpqga aelaahssll ggpqpggms aftrvnlsn  
1081 nqsakvira dpqgcrrrhs **setfsst**psa trvgntvpfg agaavggggg ssssedvkr  
1141 hssasfenvw lrpgeggap kepaklcgaa gglenglnyi dldlvkdfkq cpqectpepq  
1201 ppppppphqp lgsgessstr rssedlsaya sisfqkped rq

**Figure 2: Human IRS-2 protein sequence (SEQ ID NO: 2)**

1 maspprhgpp gpasgdgpnI nnnnnnnhS vrkcgylrkq khghkrffvl rgpgaggdka  
61 tagggsapqp prleyyesek nwrskagapk rviaIdccIn Inkradpkhk yliaIytKde  
121 yfavaaeneq egegwyralT dlVsegraaa gdappaaapa ascsaslpGa vgsSagaaga  
5 181 edsYglvapa taayrevwqv nlkpkglgqs knltgvyrIc lsartIgfVc InceqpsvtI  
241 qImnirrcgh sdsfffiEvG rsavtgpGel wmqaddsvva qnihetilea mkalkelfef  
301 rprsksqssg ssathpisvp garrhhhlvn lppsqtglvr rsrtdslaT ppaakcsscr  
361 vrtasegdgg aaagaaaaga rpvsvagspl spgpvrapls rshtlIggcr aagtkwhcfp  
421 agggIqhsrs msmpvehlpp aatSpgsIss ssdhgwgsyp pppgphIlp hplhhgpgqr  
10 481 pssgsasasg spsdpgfmsI deYgsspgdI rafcsHrsnt pesiaetppa rdgggggGefy  
541 gymtmDrpls hcgrsyrrvs gdaaqdlDrG lkrtySlTt parqrpvpqp ssasIdeytl  
601 mratfsgsag rIcPscpass pkvayhpye dygdieigsh rsssnlgad dgympmtpga  
661 alagsgsgsc rsddympmsp asvsapkqil qpraaaaaaa avpfagpagp aptfaagrtf  
721 pasgggykas spaesspedS gymrmwcgsk lsmehadgkl lpngdylnvs psdavttgtP  
15 781 pdffsaalhp ggeplrgvpg ccYssIprsy kapytcgGds dQyvlmsspV grileeerle  
841 pqaTpgptqa asafgagptq pphpvvpspV rpsGgrpegf lqqrgravrp trlsleglps  
901 lpsmhEypIp pepkspgeyi nIdfgepgar lppappla saassslls asspalslgs  
961 gtpgtssdsr qrsplsdymn ldfsspkspk pgapsghpvg sldgllspea ssypplppr  
1021 psaspssslq ppppppapge lyrlppasav ataqqpgaas slsdtgdng dytemafgva  
20 1081 atppqpiaap pkpeaarvas ptsgvkrIsI meqvsgveaf lqasqppdph rgakviradp  
1141 qggrrrhsse tfsstttvtp vspsfahnpk rhnsasvenv slrksseggv gvgpggggdep  
1201 ptsprqlqpa pplapqgrpw tpgqpggIvg cpgsggspmr retsagfqng lkyiaidvre  
1261 epglppqpqp pppplpqpgd ksswgrtrsl ggIIsavgvG strggcgpgp pgapapcptt  
1321 yaqh

25

30

Figure 3: Serine phosphorylation of IRS-1 in CHO/IR/IRS-1 cells

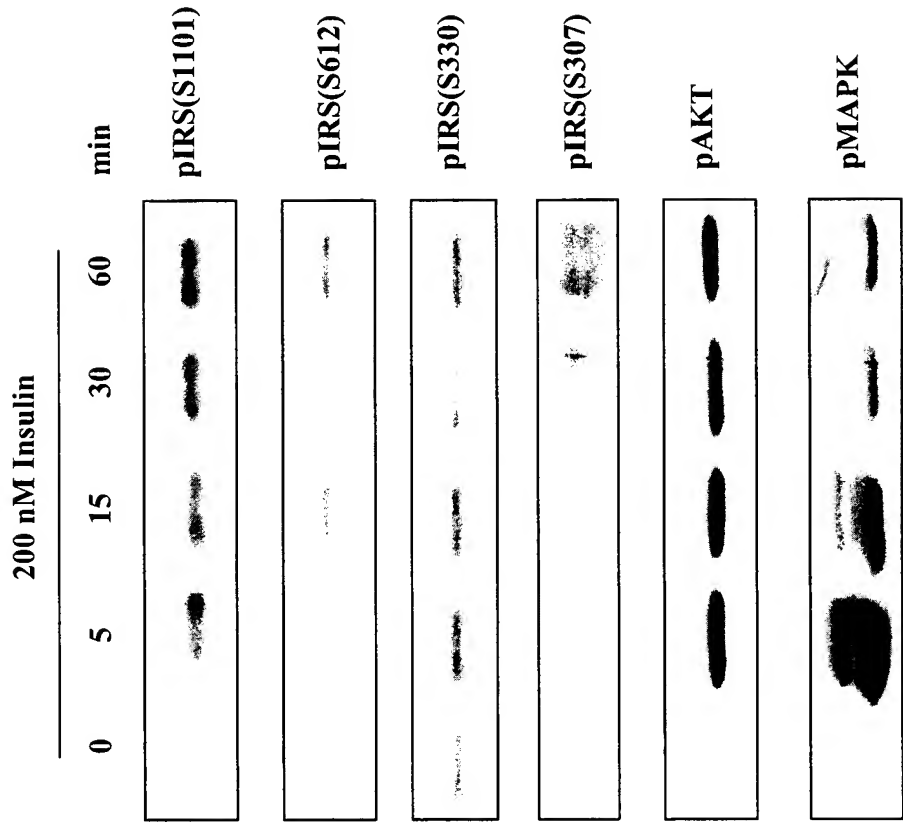
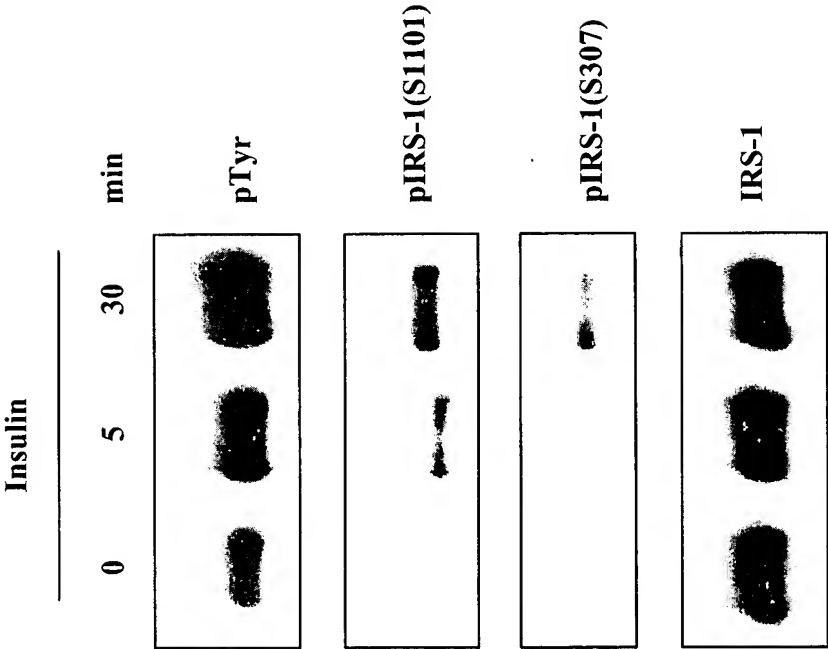


Figure 4: Phosphorylation of IRS-1 in 3T3L1 fat cells



**Figure 5: Phosphorylation of IRS-1 in L6 myocytes**

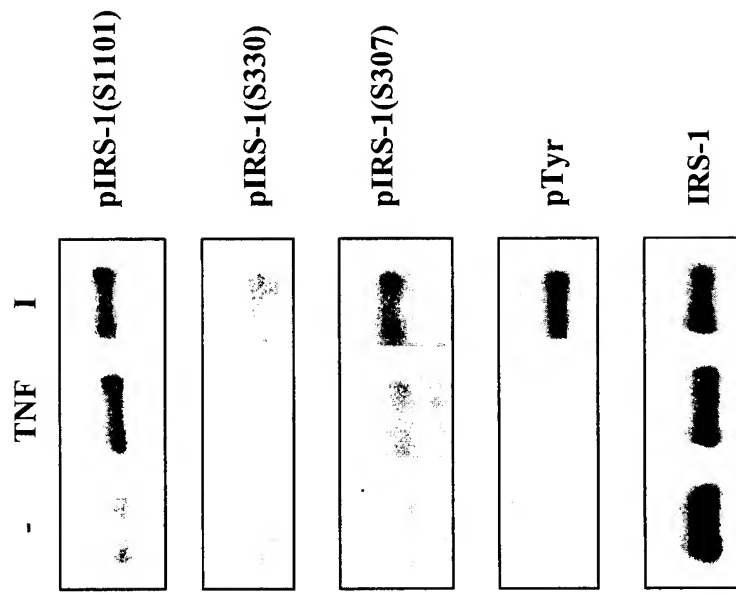


Figure 6: Specificity of pIRS-1(Ser1101) antibody

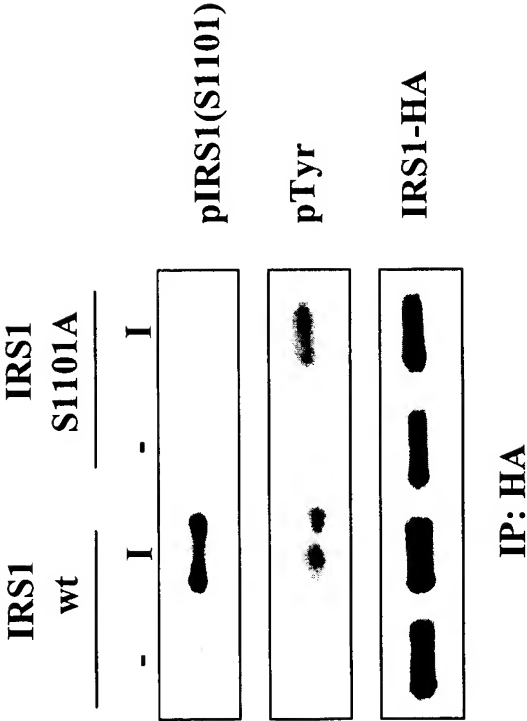
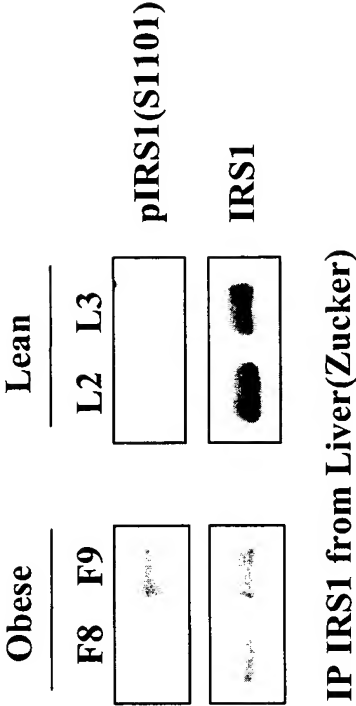


Figure 7: Phosphorylation of IRS-1 at Ser1101 in liver of Zucker rats



**Figure 8: Phosphorylation of IRS-2 at Ser1149 in CHO cells**

**IRS-1 S1101: GCRRRRHS\*SETFSSTP**

**IRS-2 S1149: GGRRRRHS\*SETFSSTT**

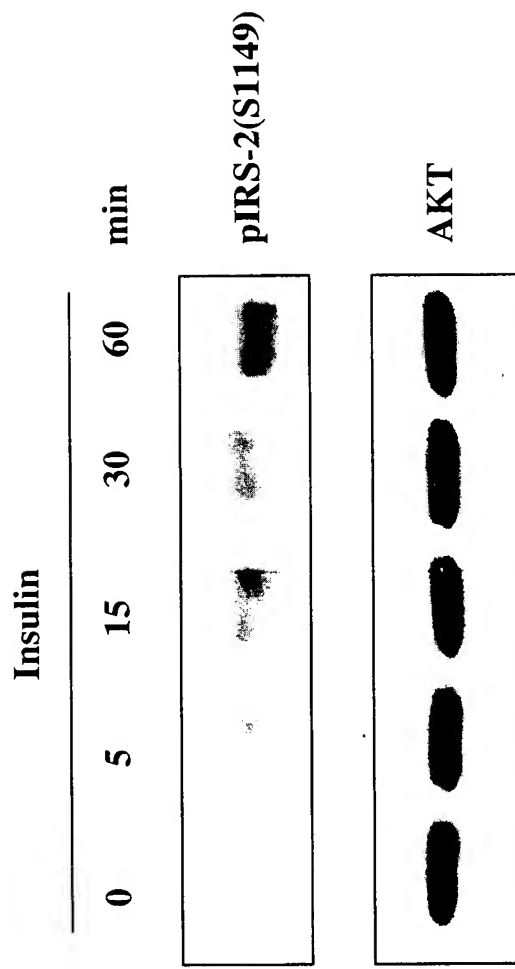




Figure 9: Phosphorylation of IRS1 at Ser1101 correlates with PKC activation

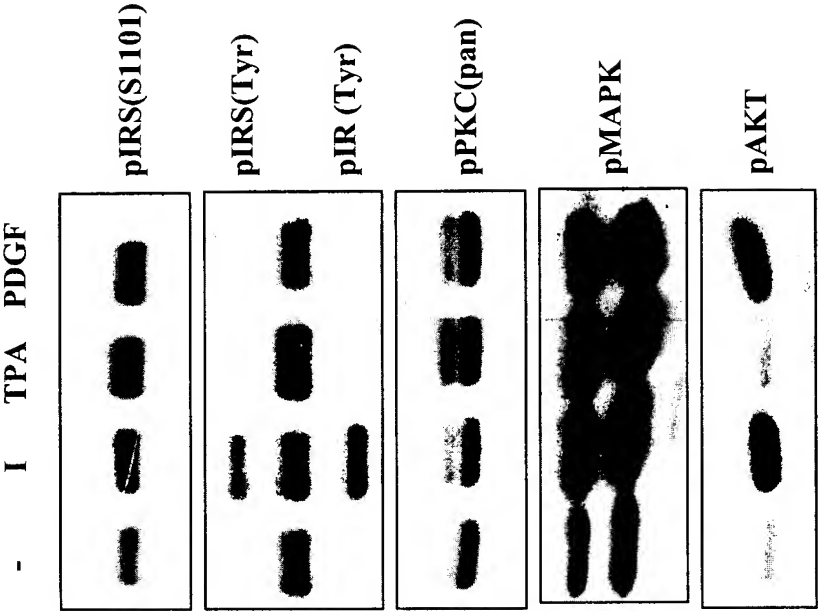


Figure 10: Phosphorylation of IRS1 at Ser1101 is blocked by PKC inhibition

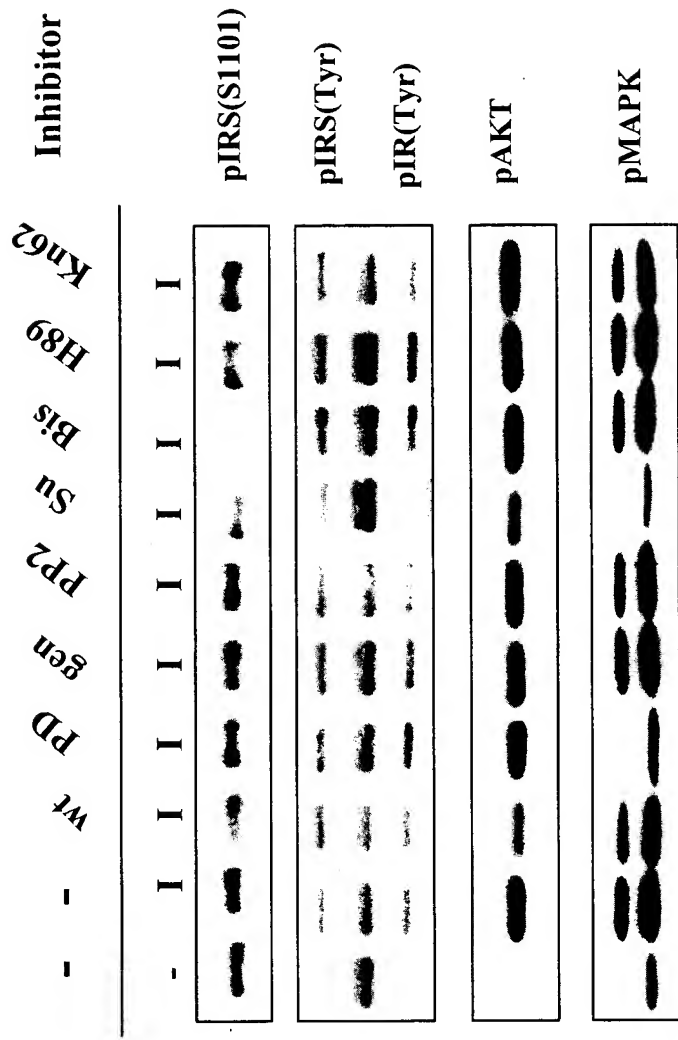


Figure 11: PKCθ kinase phosphorylates IRS-1(Ser1101) in vitro

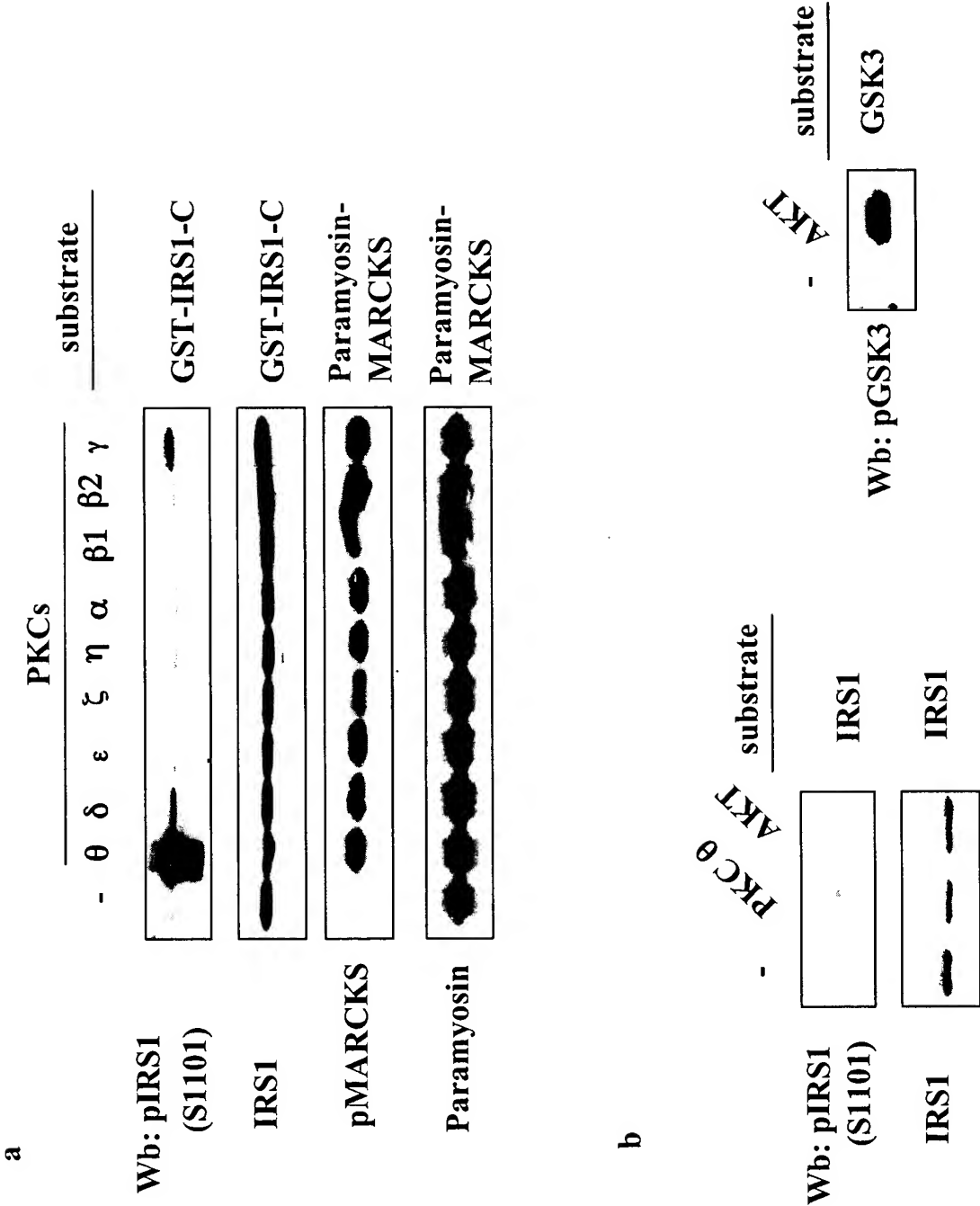
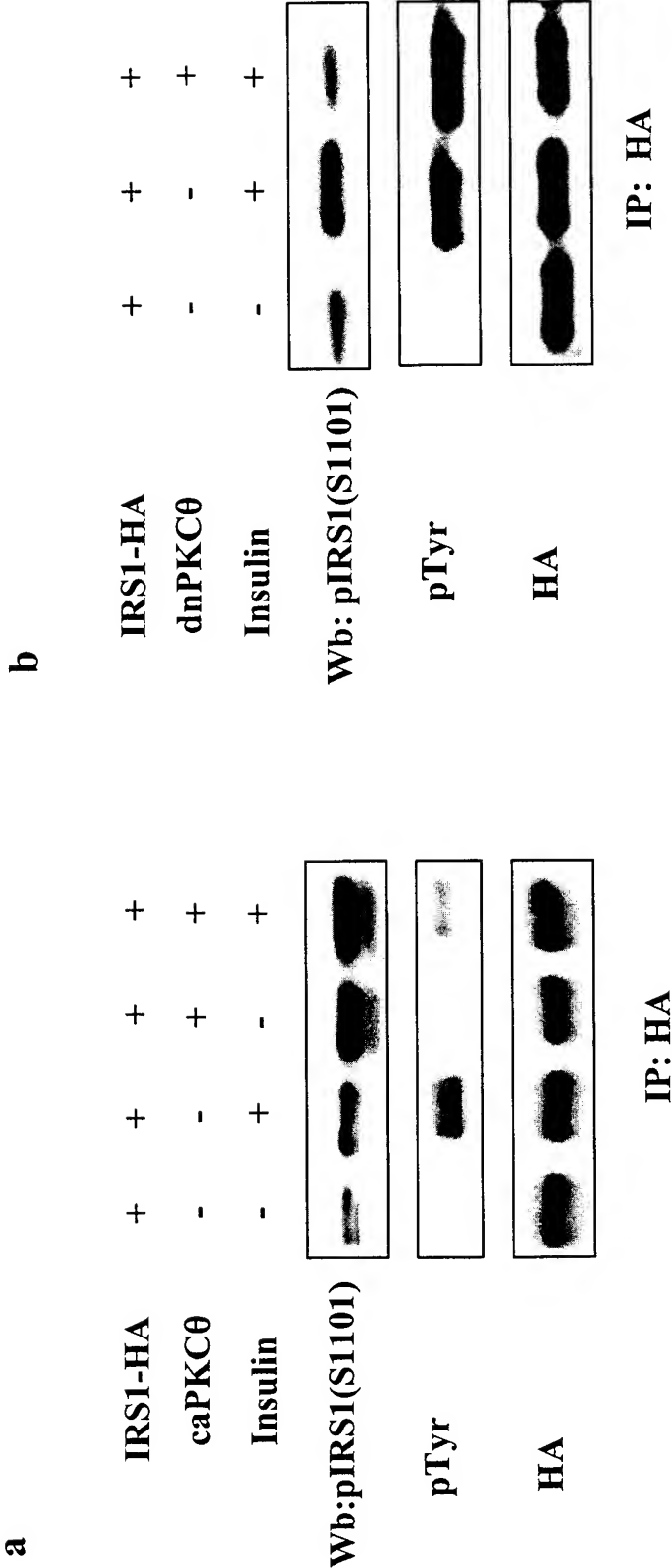


Figure 12: PKCθ kinase phosphorylates IRS-1(Ser1101) in vivo



**Figure 13: Mouse IRS-1 protein sequence (SEQ ID NO: 3)**

1 masppdtgdf sdvrkvgylr kpksmhkrff vlraaseagg parleyyene kkwrhkssap  
61 krsiplescf ninkradskn khlvalytrd ehfaiaadse aeqdswyqal lqlhnrakah  
121 hdgagggcgg scsgssgvge agedlsydtg pgpafkevwq vilkpkglgq tknligiyr  
181 cltsktisfv kinseaaavv lqlmnirrcg hsenfffierv grsavgpge fwmqvddsvv  
241 aqnmhetile amramsdefr prsksqssss csnpisvplr rhlhlnppps qvgltrrsrl  
301 esitatpas mvggkpgsfr vrassdget msrpsvdgs pvspstnrth ahrhrgssrl  
361 hpplnhrsi pmpssrcsps atspvslsss stsghgtsd clfprssas vsgpsdggf  
421 issdeygssp cdfrssfrsv tpdslghtpp argeeelsny icmggkgast laapnghyil  
481 srgngghryi pganlgtspa lpgdeaagaa dldnrfrkrt hsagtsptis hqktpsqsav  
541 asieeytemm paayppgggs ggrlpgyrhs afvpthsyte eglemhhler rgghhrpdt  
601 nlhtddgyp mspgvapvps nrkgngdyp mspksvsapq qiinpirrhp qrvdpngymm  
661 mspsgscspd igggssssss isaapsgssy gkpwtnvgg hthalphak ppvesgggkl  
721 lpctgdymnm spvgdsntss psecygppe pghkpvlsyy slprsfkhtq rpgepegar  
781 hqhlrlssss grlryatae dsssstssds lgggycgarp esslthphhh vlqphlprkv  
841 dtaaqtnsrl arptrlsld pkastlprvr eqqqqqqsssl hppepkspge yvniefgsgq  
901 pgylagpats rsspvrpp qlhpapreet gseymnmdl gpgratwqe sggvelgrig  
961 pappgsatvc rptrsvpsr gdymtmqigc prqsyvdtsp vapvsyadmr tgiaaekasl  
1021 prptgaapp sstasssvtp qgataeqath sslggpqp ggmsaftrvn lspnhnqsak  
1081 viradtqgcr **rrhssetfsa** ptragntvpf gagaavggsg ggggggsedv krhssasfen  
1141 vwlrpgdlgg vskesapvcg aaggleksln yidldaker sqdcpsqqqs lppppphqpl  
1201 gsnegnspr ssedlsnyas isfqkqpedr q

**Figure 14: Mouse IRS-2 protein sequence (SEQ ID NO: 4)**

1 masaplpgrp asgggdgpnlnnnnnnnnhs vrkcgylrkq khghkrffvl rgpgtggeda  
61 saaggspqp prleyyesek kwrskagapk rvaldcln inkradakhk yliaitykde  
121 yfavaaeneq eqegwyralt dlvsgrsge gsgtggtgsc saslpgvlgg sagaagcddn  
181 yglvtpatav yrevwqvnk pkglgqsknl tgvyrclsa rtigfvklnc egpsvtlqln  
241 nirrcghsds fffievgrsa vtgpgelwmq addsvvaqni hetileamka lkelfefrpr  
301 sksqssgssa thpivpgr rhhhlvnlpp sqtglvrrsr tdsaatppa akctscrvt  
361 asegdgaag gagtaggrpm svagsplspg pvrapsrsh tlasgaggrp skvtlapagg  
421 alqhsrsnm pvahsppaat spgslssssg hgsgsyplpp gshphlphpl hhpqgqrps  
481 gsasasgsp dpgfmsldey gsspgdlraf sshrsntpes iaetppardg sggylygms  
541 mdrplshcgr pyrvsgdga qdldrglkr tysltparq rvpqpssas ldeytlmrat  
601 fsgssgrlcp sfpasspkva ynpypedyg ieigshksss snlgaddgym pmtpgaals  
661 ggpnscksdd ympmsptsvs apkqilqprl aaalppsgaa vpappsgvgr tfpvngggyk  
721 asspaesspe ds gymrmwgc sklsmenpdp klpngdyn kspseagtag tpdfsaalr  
781 ggseglkgip ghcysslprs ykapcscsgd ndqyvlmssp vgrileerl epqatpgagt  
841 fgaaggshtq phsavgpssm rpsaiggrpe glgqrcrav rptrlslegl qlpsmqeyp  
901 lptepkspge yinidpgeag trlspapp lsaassss lssasspassl gsgtpgtssd  
961 srqrspldy mnl dpsspks pkpstrsgdt vgsmdgllsp easspypplp prpstspss  
1021 qqplppapgd lyrlppasaa tsqgptagss mssep gdngd ysemafva tppqpivapp  
1081 kpegarvasp tsglkrslm dqvsgveafl qvsqppdphr gkviradpq **ggrrrhsset**  
1141 **fsstttvtpv** spsfahnscr hnsasvenvs lrkssegsst lgggdeppts pgqaqplvav  
1201 ppvpqarpwn pgqpgalgc pggssspmrr etsvgfngl nyiaidvrge qgslaqsqq  
1261 pgdknswrt rslgllgtv ggsgasgvcg gpgtgalpsa styasidfls hhlkeatvk  
1321 e